

Solvent Fractionation of Girard T Derivatives of Carbonyl Compounds Using Dimethyl Sulfoxide

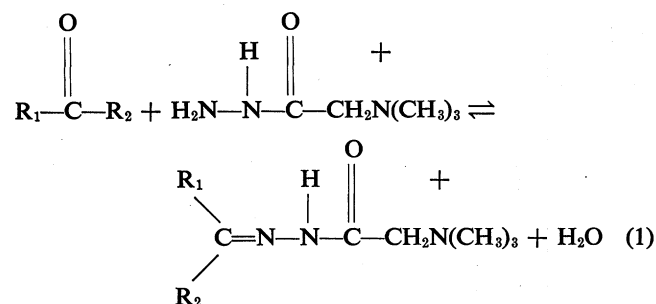
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IN THE COURSE of our investigation of the chemical composition of cigar smoke we recently isolated a neutral fraction by silicic acid column chromatography which was shown to contain at least 30 compounds by gas chromatographic analysis. Attempts to obtain the pure components of this fraction by further chromatographic methods were unsuccessful. Therefore, we attempted to separate this fraction into a carbonyl and noncarbonyl subfraction.

Isolation of the carbonyl compounds via the corresponding 2,4-dinitrophenyl hydrazones was ruled out because of the difficulties encountered in regenerating the free carbonyl compound. Reaction of the carbonyl compounds with Girard T reagent (tetramethyl ammonium acetyl hydrazide) to give a polar hydrazone (Equation 1), which can be separated from relatively nonpolar unreacted compounds by solvent partitioning, appeared to be a desirable alternate route for this separation:



We used this method to separate farnesyl acetone (6,10,14-trimethyl-5,9,13-pentadecatriene-2-one) from the C_{20} -terpene alcohol, phytol [these two compounds were previously identified in this fraction (1)]. We did not obtain encouraging results using reaction conditions described in the literature (2). When the two compounds were subjected to treatment with Girard T reagent in absolute ethanol followed by the addition of water (giving a 15% aqueous ethanol solution) and then extraction of the unreacted phytol with hexane, an appreciable amount of farnesyl acetone was also recovered

in the hexane layer. That the free farnesyl acetone found in the hexane was a product of hydrolysis of the already formed hydrazone and not the result of the incomplete reaction of the Girard reagent with the ketone was demonstrated in the following experiment. Farnesyl acetone was reacted with the Girard reagent in absolute ethanol, the unreacted Girard reagent was precipitated by adding hexane to the solution, the precipitate was filtered, and the filtrate was analyzed by gas chromatography. No farnesyl acetone could be detected in the hexane.

To delineate the effect of hydrolysis, a standard mixture (containing compounds similar to those we believed to be present in our tobacco sample) was subjected to a wide variety of reaction and separation conditions described in the literature. The results of these experiments are given in Table I. In all cases hydrolysis of the hydrazone of farnesyl acetone and octanone is evident even when the amount of water introduced to produce an immiscible polar layer (Case 1) is kept at a minimum. To avoid this problem we decided to explore reaction conditions using a nonaqueous system. We reacted our known mixture with Girard T reagent in dimethyl sulfoxide (DMSO) for 1 hour, followed by extraction of the unreacted compounds with hexane. The separation, although not complete, was better than we had obtained using aqueous systems. The presence of carbonyl compounds in the noncarbonyl fraction could be avoided completely. With six extractions, only 65% of the geraniol was recovered (which is still the best separation obtained).

The cigar smoke fraction was reacted with the Girard T reagent as follows: The condensate (dry weight approximately 1.0 gram) was dissolved in 10 ml of DMSO, 0.5 gram of Girard T reagent was added, and the solution stirred for 3 hours at room temperature. The DMSO solution was then extracted with 6×10 ml of petroleum ether. The petroleum ether was concentrated and analyzed by gas chromatography. At least 20 peaks were apparent in the chromatogram of which phytol (a methyl ethyl phenol) and dihydrocinnamyl nitrile were identified by spectroscopic examination of the corresponding peak eluates. The DMSO solution was diluted with an excess of water, heated to 50°C for 1 hour and then extracted with hexane. Farnesyl acetone, solanone (2-methyl-5-isopropyl-1,3-nonadiene-8-one), and a

- (1) S. Osman and J. Barson, *Tob. Sci.*, **X**, 85 (1966).
(2) O. H. Wheeler, *Chem. Rev.*, **62**, 205 (1962).

Table I. Summary of Girard T Reaction in Various Solvent Systems

Reaction solvent	Extraction solvent	H ₂ O added in isolation step, %	% Unreacted carbonyl ^a			Geraniol recovered, % ^c
			Citral	2-Octanone	F.a. ^b	
Absolute ethanol	Petroleum ether	15	0	10	15	50
Absolute ethanol	Petroleum ether	30	0	40	49	70
Absolute ethanol	Methylene chloride	15	0	40	43	82
<i>t</i> -Butanol	Petroleum ether	>100	55	90	93	55
Dimethyl sulfoxide	Petroleum ether	0	0	0	0	65

^a Free carbonyl compounds that are extracted along with geraniol.

^b Farnesyl acetone.

^c By extraction with equal volumes of hexane $6 \times$.

C-17 methyl ketone (not completely characterized) were identified in this fraction. There was no evidence of compounds such as phytol in this fraction, and none of the carbonyl compounds were apparent in the gas chromatogram of the hexane extract containing the phytol. Until both hexane fractions are completely characterized, however, we cannot state with certainty the degree of separation.

In conclusion, many Girard T hydrazones are susceptible to hydrolysis even under mild conditions. This problem limits the use of the Girard reagent for many separations of carbonyl from noncarbonyl compounds. A nonaqueous system has been developed to overcome this problem. Al-

though poor partitioning factors may arise in the nonaqueous system these can be minimized by increasing the number of extractions.

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